

Improved Mobilization of Exogenous Mesenchymal Stem Cells to Bone for Fracture Healing and Sex Difference.

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Public Summary:

The current study used a clinically relevant preclinical fracture model of both sexes and found that treatment with a novel hybrid compound, LLP2A-Ale, that mobilizes endogenous MSCs to bone remodeling sites, with transplanted MSCs, increased engraftment of MSCs to the fracture site. This was associated with augmented bone formation that resulted in improved bone strength. In addition, we found that increased mobilization of exogenous MSCs to fracture sites accelerated endochondral bone formation partially through paracrine signaling to enhance bone tissue regeneration. These results are important for targeted delivery of MSCs for fracture repair through direct cell differentiation and paracrine mechanisms.

Scientific Abstract:

Mesenchymal stem cell (MSC) transplantation has been tested in animal and clinical fracture studies. We have developed a bone-seeking compound, LLP2A-Alendronate (LLP2A-Ale) that augments MSC homing to bone. The purpose of this study was to determine whether treatment with LLP2A-Ale or a combination of LLP2A-Ale and MSCs would accelerate bone healing in a mouse closed fracture model and if the effects are sex dependent. A right mid-femur fracture was induced in two-month-old osterix-mCherry (Osx-mCherry) male and female reporter mice. The mice were subsequently treated with placebo, LLP2A-Ale (500 µg/kg, IV), MSCs derived from wild-type female Osx-mCherry adipose tissue (ADSC, 3×10^5 , IV) or ADSC + LLP2A-Ale. In phosphate buffered saline-treated mice, females had higher systemic and surface-based bone formation than males. However, male mice formed a larger callus and had higher volumetric bone mineral density and bone strength than females. LLP2A-Ale treatment increased exogenous MSC homing to the fracture gaps, enhanced incorporation of these cells into callus formation, and stimulated endochondral bone formation. Additionally, higher engraftment of exogenous MSCs in fracture gaps seemed to contribute to overall fracture healing and improved bone strength. These effects were sex-independent. There was a sex-difference in the rate of fracture healing. ADSC and LLP2A-Ale combination treatment was superior to on callus formation, which was independent of sex. Increased mobilization of exogenous MSCs to fracture sites accelerated endochondral bone formation and enhanced bone tissue regeneration. Stem Cells 2016;34:2587-2600.

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